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Use of quality rapid diagnostic testing for safe blood transfusion in resource-limited settings

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Abstract

Blood safety in sub-Saharan Africa is jeopardized by multiple and diverse factors, including the predominance of high-risk family/replacement donors and the high prevalence of transfusion-transmissible infections (TTIs). Thus, stringent diagnostic strategies are vital. Western blotting is costly and technically demanding, and nucleic acid testing technologies, which have been reported to reliably reduce the rate of TTI, are not available in resource-limited settings. Therefore, there is a need for reliable and affordable testing alternatives in these settings. Rapid diagnostic testing has been widely adopted in developing countries, but, for effectiveness in blood safety, highly sensitive tests and the strict selection of low-risk blood donors are indispensable. Although the pre-serological window period remains a source of residual risk for transmission of TTIs during blood transfusion, the combination antigen–antibody rapid tests could contribute significantly to shortening the window period. Thus, despite its limitations, rapid diagnostic testing continues to contribute significantly to blood safety, as a cost-effective means of enhancing screening for TTIs and reducing their transmission in resource-limited rural settings.

Keywords: HBV, HCV, HIV, rapid diagnostic testing, resource-limited setting, syphilis, TTI
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Introduction

Screening for blood-transmissible pathogens is a critical aspect of blood safety. Where effective screening programmes exist, the risk of transmission of transfusion-transmissible infections (TTIs) has been reported to progressively and significantly decrease [1,2]. This has been clearly demonstrated in western countries, where the most reliable screening methods are used, including nucleic acid amplification testing technologies, which allow for very early detection of various infectious agents [3]. Other confirmatory tests often used include western blot assays, line immunoassays (LIAs), recombinant immunoblot assays, indirect fluorescent antibody assays, and ELISAs. Unfortunately, these technologies are only feasible in major African cities, where external funding is obtainable.

Paradoxically, blood safety in these resource-limited settings (RLSs), and especially in sub-Saharan Africa (SSA), is compromised by several factors [4], including the highest prevalence of TTIs and the chronic shortage of reagents for their diagnosis. The major TTIs described include human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), syphilis, and malaria. Hence, the WHO recommends that all blood for transfusion in RLSs be mandatorily screened for HIV, HBV, HCV, and syphilis [5], with either a combination of HIV antigen–antibody or HIV antibodies, hepatitis B surface antigen (HBsAg), a combination of HCV antigen–antibody or HCV antibodies, and specific treponemal antibodies, respectively [6]. Despite this, several countries are unable to screen all donated blood for one or more of these markers [5].

Another major issue concerns voluntary, non-remunerated and regular blood donors, who are reported to have the lowest rates of TTI [7]. However, in these RLSs, family/replacement and, in some cases, paid donors, with high risks for TTI, provide 70–90% of donations [4,8–10]. Although these family and replacement donors are more cost-effective for RLSs [8,11] and more easily manageable than a centralized 'western model' based on a 100% voluntary, non-remunerated and regular blood donor system [8,12], it must be emphasized that increased blood safety is only achievable with low-risk

blood donors. In 2010, Choudary reported a 1–2 per 1000 risk for blood recipients of contaminated blood of acquiring viral, bacterial or parasitic infections [13], even with very low pathogen load. Hence, it is vital to meticulously select safe blood donors and ensure the use of quality screening methods.

Even in RLSs, the use of affordable alternative screening methods such as rapid diagnostic testing will contribute significantly to blood safety, including in the more rural settings, where small numbers of daily tests (e.g. <20 samples/day) are performed. A recent study in Tete, in Mozambique, has clearly illustrated the need for and effectiveness of the consistent use of quality-assured rapid diagnostic tests (RDTs) in screening donated blood [14].

Rapid diagnostic testing is currently available for the screening of various pathogens, including HIV, HBV, HCV, syphilis and malaria infections, and newer technologies are being developed continuously. These are simple instrument-free assays that may be performed by personnel who have received very little training, and no laboratory facilities are required. The test kits are generally low in cost, with prices in the WHO bulk procurement scheme ranging from US $0.40 to US$2.00 per test. In addition, the kits are easy to store (room temperature, with no need for refrigeration), and require very short intervals (10–30 min) to provide results. These characteristics have rendered rapid diagnostic testing especially user-friendly in RLSs. Consequently, rapid diagnostic testing has been integrated into, and served as a point-of-care tool, in various healthcare programmes. Alternative testing strategies and algorithms have also been developed for pathogen screening and confirmation based on quality rapid diagnostic testing, both for transfusion and other services, especially where only few blood units are collected [15]. A typical scenario in SSA would be blood transfusion; this is often an urgent clinical decision requiring immediate results, which rapid diagnostic testing could provide within 30 min. Thus, rapid diagnostic testing is indispensable in such situations.

This review focuses on alerting clinicians and heads of transfusion services to the current pitfalls of transfusion services in RLSs, and the use of rapid diagnostic testing as an alternative for providing safe blood in these settings.

Pitfalls in Blood Transfusion Services in RLSs

Blood transfusion services in RLSs, especially in SSA, are inadequate in all aspects of the blood safety chain, from policy development through blood donor selection to the appropriate use of blood products [16]. In 2006, only 22 of the 46 member states in the African Region of the WHO had developed policies for blood transfusion [17], and implementation has been equally slow. The lack of national coordination of designated blood transfusion budgets, trained staff, donor recruitment programmes and national testing strategies, the lack of national guidelines for the clinical use of blood and the lack of haemovigilance and quality management programmes all contribute to hampering blood safety in these RLSs. In addition, the high disparity in funding systems and financing mechanisms is an issue of concern. Some RLSs have benefited from external funding, including the President's Emergency Plan for AIDS Relief (PEPFAR) and from the CDC, Atlanta, and hence may boast of reasonably reliable transfusion services, but the issue of sustainability post-funding remains.

Performance and Limitations of Rapid diagnostic Testing in Blood Transfusion Safety in RLSs

Principles of rapid diagnostic testing

RDTs are based on different principles, of which four major types have been described (see Editorial). Many of these tests have an internal sample addition control that validates each test run. Whole blood, serum, plasma, and even finger-prick blood specimens, saliva or oral fluids have been used with these tests. Various test kits based on these principles are commercially available for use in RLSs, and lateral-flow immunochromatographic assays seem to be most current.

A few organizations, including the WHO and the US Food and Drug Administration, carry out evaluations of test kits based on criteria set by the WHO. They include: the speed with which results are obtained (<30 min); accuracy (sensitivity and specificity of >99% and >98%, respectively); minimal specimen volume; variability in specimen type (whole blood, plasma, and serum); ease of use (no specialized equipment); and stability of the reagents at ambient temperatures or between 2°C and 8°C [18]. Details of some currently available quality RDTs, based on these criteria, are shown in Table 1 [19–21]. For further reading on RDT, see Table 2.

RDTs for HIV

Many RDTs for HIV utilize the gp41 antigen as the target antigen for detecting HIV. Serological markers such as antibodies to HIV-1, including group O, to HIV-2, and to the p24 antigen, which appears early in the infection, are detected, as well as viral RNA when possible. Thus, the diagnostic tests contain antigens to specific HIV proteins of one group or subtype, hence may vary in performance, according to the [9] HIV strain being detected [22].

High rates of false-positive HIV results have been reported in several studies [23–25], usually because of the relatively low

TABLE 1. Some available quality rapid diagnostic test kits for transfusion-transmissible infections [19–21] (the selection of examples is based mainly on high sensitivity and/or specificity)

Name	Manufacturer	Pathogen	Sensitivity (%)	Specificity (%)	Performance evaluation criteria
Determine HIV1/2	Abbott Laboratories	HIV	100	99.6	WHO [19]
HIV 1/2 STAT-PAK	Chembio Diagnostic Systems	HIV	99.7	99.3	WHO [20]
HIV 1/2 STAT-PAK Dipstick	Chembio Diagnostic Systems	HIV	99.0	100	WHO [20]
Uni-Gold HIV-1/HIV-2	Trinity Biotech	HIV	100	100	WHO [20]
Immunocomb II HIV 1&2 BiSpot	Organics	HIV	100	99.7	WHO [20]
Retrocheck HIV 1&2/Core HIV 1&2	Qualpro Diagnostics/Core Diagnostics	HIV	100	99.1	WHO [20]
DoubleCheckGold HIV 1&2	Organics	HIV	100	99.3	WHO [20]
OraQuick HIV-1/2	OraSure Technologies	HIV	100	99.2	WHO [20]
Multispot HIV 1/2	Bio-Rad Laboratories	HIV	100	99.93	FDA [19]
Determine Syphilis TP	Abbott Laboratories	Syphilis	100	98.6	WHO [19]
HCV Tri Dot	J. Mitra & Co.	HCV	100	91.5	WHO [19]
HCV SpoT	Genelabs Diagnostics	HCV	100	93.7	WHO [19]
SeroCard HCV	Trinity Biotech	HCV	98.5	100	WHO [19]
Determine HBsAg	Abbott Laboratories	HBV	100	100	WHO [19]
Dainascreen	Abbott Laboratories	HBV	100	100	WHO [19]
SD BioLine HBsAg (One Step HBsAg Test)	Standard Diagnostics	HBsAg	97.95	100	ICBS [21]
Assure HBsAg Rapid Test	MP Biomedicals Asia Pacific	HBsAg	97.95	100	ICBS [21]
Quick Chaser HBsAg	Mizuho Medy	HBsAg	97.95	100	ICBS [21]

FDA, Food and Drug Administration; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; ICBS, International Consortium for Blood Safety.

TABLE 2. References on quality rapid diagnostic tests for further reading

Pathogen	References
HIV	Point-of-Care HIV Testing Using Rapid HIV Test Kits: Guidance for Health-Care Professionals www.who.int/diagnostics_laboratory/evaluations/hiv/en/ Rapid immunochromatographic detection by amplification of the colloidal gold signal www.who.int/diagnostics_laboratory/evaluations/hiv/en/
HIV	http://jcm.asm.org/content/48/8/2836.full.pdf+html
Trypanosoma	
Syphilis	Sena AC, White BL, Sparling PF. Novel treponema pallidum serologic tests: a paradigm shift in syphilis screening for the 21st century. *Clin Infect Dis* 2010; 51: 700–708. cid.oxfordjournals.org/content/51/6/700.full Diagnostic testing for syphilis www.uptodate.com/contents/diagnostic-testing-for-syphilis
HCV	WHO Hepatitis C test kit evaluations www.who.int/diagnostics_laboratory/evaluations/hepc/en/ Smith BD, Drobeniuc J, Jewett A *et al.* Evaluation of three rapid screening assays for detection of antibodies to hepatitis C virus. *J Infect Dis* 2011; 204: 825–831. www.natap.org/2011/HCV/JDis2011-Smith-825-31.pdf O'Connell RJ, Gates RG, Bautista CT *et al.* Laboratory evaluation of rapid test kits to detect hepatitis C antibody for use in predonation screening in emergency settings. *Transfusion* 2012; Jul 23. doi: 10.1111/j.1537-2995.2012.03770.x. [Epub ahead of print] CBS: HCV test kit (2006) http://www.icbs-web.org/page30.html
HBsAg	http://www.rapid-diagnostics.org/files/HBV-Manufacturers-website.rtf www.who.int/diagnostics_laboratory/evaluations/hepb/en/ http://www.icbs-web.org/page30.html (2010)
HIV, HCV, HBV, syphilis	WHO 2010, http://www.who.int/bloodsafety/ScreeningDonatedBloodforTransfusion.pdf

HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus.

specificities of some test kits, despite very high sensitivities. Low specificities of HIV antibody screening tests may also result from tropical infections that cause B-cell activation, such as human African *Trypanosoma* infections, resulting in false-positive results [26]. False-negative results also represent a challenge [25], exacerbated by poor staff training and subjectivity in interpreting faint RDT results [24].

RDTs for HBV

The earliest HBV serological marker is its surface antigen HBsAg, but others develop in the course of the infection. Thus, one main target in HBV screening includes serology of HBsAg; however, routine screening for its core antibody (anti-HBc) is not recommended, because of non-specific results [6].

Most RDTs for HBV are based on agglutination or lateral-flow principles, and qualitatively detect the presence of HBsAg. These are also available for detecting other HBV serological markers, such as the HBe antigen (HBeAg) and antibodies to HBs, HBc and HBe. Various improvements are being made to these lateral-flow assays for HBV. As declared in one analysis in 2008 [27], 'the major challenge for HBsAg rapid tests is to detect the low levels of the target antigen that are present in a relatively high proportion of asymptomatic blood donors in order to achieve a clinical sensitivity similar to that of enzyme immune-assays (EIA)'. With the wide genetic diversity in HBV (genotypes A–H), there is high antigenic variation of HBsAg, and a need for high antigen concentrations of some variants in order for them to be detected with commercial kits. An

evaluation of various HBsAg assays using panels from the International Consortium on Blood Safety showed low analytical sensitivities of RDTs for HBsAg detection, as shown by 13 of 19 RDTs not detecting International Consortium on Blood Safety dilutions as positive, despite having high specificities [21]. Thus, sensitivity remains an issue for current HBV RDTs (HBsAg), despite excellent specificity. This emphasizes the continuous quest to improve the sensitivity of RDTs, which is indispensable for blood safety. An example of such an improvement is the new HBsAg rapid immunochromatographic assay based on the signal amplification system, which has been evaluated and shown to have enhanced sensitivity [27].

RDTs for HCV

The laboratory diagnosis of HCV infection consists of detecting anti-HCV antibodies in the blood, followed by the confirmation of reactive samples with LIAs. Anti-HCV antibodies are detectable in approximately 90% of cases by 12 weeks of infection [28]. The number of available HCV antibody tests, including simple/rapid tests, has increased in recent years, but rapid diagnostic testing for HCV has been reported to be less sensitive than enzyme immunoassays (EIAs) [29,30]. A recent evaluation of anti-HCV RDT performance by Smith *et al.* [31] confirmed low sensitivities, but, interestingly, the recently US Food and Drug Administration-approved OraQuick HCV Rapid Antibody Test was reported to perform comparably to EIA techniques [32]. Nevertheless, serological screening has considerably reduced HCV transmission through blood transfusion [6].

RDTs for screening for syphilis

Several methods are used for the diagnosis of syphilis; some require the use of specific treponemal antigens, some use rapid point-of-care tests, and others use EIAs as well as chemiluminescence assays. Non-treponemal tests are also used, including the old rapid plasma reagin test, which uses phospholipid (non-treponemal) antigens, the Venereal Disease Research Laboratory test, and the toluidine red unheated serum test, all of which are not only low in cost, but are also easy to perform. However, they require treponemal-based confirmation, because detectable antibodies can be produced by other inflammatory conditions, and their sensitivities vary with the type of test and stage of infection. Some treponemal tests include microhaemagglutination assays, particle agglutination assays, haemagglutination assays, and the fluorescent treponemal antibody absorption assay.

Several rapid syphilis tests are available worldwide that may be used with serum, plasma, or whole blood specimens [33]. These are highly sensitive and specific [33,34], as most detect both IgM and IgG. Although RDTs used in screening for syphilis infection have been reported to be highly sensitive, they cannot distinguish between active and treated syphilis, so false-positive reactions are possible [35]. Thus, positive results need to be confirmed with quantitative non-treponemal testing to determine recent infection and response to therapy.

Confirmation testing

The confirmation of RDT results is of relevance for issuing accurate results to blood donors, as well as for purposes of acquiring accurate epidemiological data; for blood safety, sensitivity is of the utmost importance. Where no established quality systems exist in RLSs, confirmation is not necessary, because all reactive blood units should always be discarded. However, in settings with an established quality system, the WHO recommends repeat testing, in duplicate, of the same sample and with the same assay before conclusions are drawn [6]. Furthermore, repeat testing may be performed with an alternative assay, either an RDT or an EIA [24,36]. Indeed, the WHO established an HIV diagnostic algorithm that has been adapted in various countries of RLSs for confirmation of antibodies to HIV. It must be noted here that confirmation rates are generally very low for HCV [37], although the rate of confirmation of most HBsAg RDT results is >90%, suggesting that confirmation with an alternative screening assay may not be necessary. More recently, a dual-path platform RDT based on the parallel detection of both treponemal and non-treponemal lines was evaluated in China, and showed reasonably high sensitivities and specificities with different specimen types (whole blood, plasma, and finger-prick blood), thus serving as both a screen and a confirmatory test [38]. This is a promising alternative for syphilis diagnosis in RLSs.

The main issue with TTI transmission is the window period, which allows for residual risks in blood transfusion, and combination antigen–antibody RDTs would shorten this [39], although they may still be costly for RLSs. In any case, very sensitive assays for TTIs are crucial for blood safety.

Discussions and Conclusions

Today, western blotting remains costly and technically cumbersome for RLSs, and nucleic acid amplification testing remains inaccessible to and unaffordable for most countries, especially of SSA. In this light, testing strategies including simple rapid tests are indispensable, with the possibility of using serum, plasma, whole blood and even saliva in screening for different pathogens.

RDTs are not only cheaper than algorithms based on ELISA and western blot methods, but have also been reported to have comparable effectiveness [40,41]. Furthermore, a few

systematic evaluations of rapid HIV tests with non-B subtypes of HIV-1 group M and group O and HIV-2 have established that most tests adequately detect all subtypes of group M, but that their performance is more variable with group O and HIV-2 strains [22]. Interestingly, others have reported low levels of analytical sensitivity for RDTs [23,42]. In a field trial in Uganda, using an algorithm of three rapid HIV tests, of the weakly positive results on one or more of the three tests, 94.1% were negative or indeterminate on EIA or western blotting [23], further raising issues of sensitivity. Indeed, in one study in Cameroon, Tagny *et al*. demonstrated that using a combination antigen–antibody test could prevent 55 HIV transmissions per 10 000 donations of blood missed by RDTs [43]. In another study, conducted in KwaZulu Natal (South Africa), an increase was observed in the sensitivity of rapid diagnostic testing, from 68.7% to 93.5%, after a change of test brands [44]. Unfortunately, these variations in performance between RDTs are influenced by their quality, which depends on their costs; the lowest-performing assays tend to be low-cost, because they are neither evaluated nor approved by credible institutions. The lack of rigorous standards in the laboratory and untrained staff also contribute to inaccurate RDT results [44].

Recent WHO data indicated that, of 155 countries performing 100% screening for HIV, only 71 screened for HIV in a quality-assured manner [45]. Thus, quality assurance and quality control issues are other problems that continue to leave persistent gaps in the blood safety chain in RLSs. It is vital that quality assurance procedures be applied rigorously, and that procedures for detecting errors be included in all testing protocols, to maximize the accuracy of the laboratory results. Where possible, laboratories should participate in annual external quality assessments. Furthermore, the efforts to develop alternative, easily accessible and affordable, in-country-adapted technologies, including nucleic acid amplification testing technologies, should be fostered, to provide safe blood for all.

Transparency Declaration

The author declares no conflicts of interest.

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